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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,472	04/16/2004	Michelle L. Monje	STAN-303	1490

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
06/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,472	MONJE ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,8,14,21 and 22* is/are pending in the application.

4a) Of the above claim(s) *7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,14,21-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 March 2009 has been entered.

Status of Claims

2. The amendments filed on 26 January 2009 and 31 March 2009 have been entered into the record and has been fully considered.

3. Claim 1 is amended. Claim 13 is canceled. New claim 22 has been added.

4. Claims 1, 3-5, 14 and 21-22, drawn to a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation, are being considered for examination in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

5. Upon consideration of the Applicant's amendment, all claim objections and rejections, not reiterated herein have been withdrawn, as overcome by cancellation and/or amendment of claims (26 January 2009).

6. Upon consideration of cancellation of claim 13, rejection under 35 USC § 112, second paragraph is withdrawn.

7. Upon consideration of the amendment and Applicant's persuasive arguments in view of Exhibit A showing that neurogenic inflammation is associated with peripheral nervous system; and in view of Exhibit C to explain that the Wright compounds would not cross the blood brain barrier (BBB), rejection under 35 USC § 102 (b) is withdrawn.

8. Upon consideration of the amendment to claims with new limitations, and Applicant's persuasive argument in view of Exhibit B, rejection of claims under 35 USC § 103 is withdrawn.

New Rejections

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3-5, 14, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 is rejected for reciting the term "neurogenesis capacity" that is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what structural and/or functional properties are encompassed by this phrase.

11. Claims 3-5, 14, 21-22 are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3, 14, and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 955-962, 2002), and Kyrkanides et al. (Mol Brain Res. 104: 159-169, 2002).

14. The claims recite a method of reducing loss of neurogenesis capacity resulting from neuroinflammation due to cranial ionizing irradiation in an individual, comprising contacting the individual with non-steroidal anti-inflammatory drug (NSAID), indomethacin (claims 1, 3, 21) such that it crosses the BBB, wherein the neurogenesis is associated with the central nervous system (claim 14), and the loss of neurogenesis is manifested as progressive decline in cognition (claim 22).

15. Kondo et al. teach the effect of indomethacin in gerbils induced with cerebral ischemia leading to neuroinflammation. Indomethacin resulted in delayed hippocampal neuronal cell death and reduced apoptosis detected by TUNEL assay (abstract; Figures 2, 3), thereby reducing loss of neurogenesis capacity. The reference also teaches that indomethacin crosses the BBB (page 352, col 1, para 2).

16. Kondo et al do not teach the administration of NSAID to an individual subjected to cranial irradiation promoting neuroinflammation and a reduction in loss of neurogenesis.

17. Plevova teaches that ionizing radiation results in an inflammatory reaction and cellular damage, an effect that is inhibited by coricosteroids and NSAID (abstract). Furthermore, as evidenced by Monje et al. cranial irradiation results in neuroinflammation, activation of microglial cells and loss of neurogenesis, resulting in long-term debilitating cognitive decline (abstract; page 955, para 1; page 958, col 1).

18. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to substitute the method of reducing loss of neurogenesis capacity using NSAID or indomethacin due to cerebral ischemia as taught by Kondo et al. for a method of reducing loss of neurogenesis due to neuroinflammation induced by cranial irradiation in an individual as taught by Plevova and Monje et al. The person of ordinary skill in

the art would have been motivated because both cerebral ischemia and cranial radiation induce neuroinflammation and indomethacin is shown to prevent the neuronal damage and loss of neurons in both instances. Furthermore, the person of ordinary skill would be motivated to use indomethacin in models of cranial irradiation based on evidence showing that cyclooxygenase 2 or COX-2 mRNA is induced in the mouse brain following irradiation in a dose dependent manner, as well as in ischemic cerebral injury (Kyrkanides et al. Figure 1A; page 159, col 2), and indomethacin is a known COX-2 inhibitor. The person of ordinary skill in the art would have expected success because the cytotoxic and inflammatory effects of irradiation as well as the anti-inflammatory effects of indomethacin were well known at the time the invention was made.

19. Claims 1, 3-5, 14, and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tada et al. (Neurosurgery 41: 209-219, 1997 – online publication 1-18 pages), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 955-962, 2002).

20. The claims recite a method of reducing loss of neurogenesis capacity resulting from neuroinflammation due to cranial irradiation in an individual, comprising contacting the individual with non-steroidal anti-inflammatory drug (NSAID), indomethacin (claims 1, 21) such that it crosses the BBB, wherein the neurogenesis is associated with the central nervous system (claim 14), and the loss of neurogenesis is manifested as progressive decline in cognition (claim 22).

The claims further recite that the inflammation and microbial activation results from cranial ionizing radiation, and the anti-inflammatory agent is contacted prior or subsequent to the irradiation (claims 3-5).

21. Tada et al. teach the effect of the anti-inflammatory agent dexamethasone on radiation induced brain damage in Japanese primates (Abstract; Discussion, para 2, 4). The results demonstrate that primates administered with dexamethasone 2 days before cranial irradiation and continued for 7 days after irradiation, display significant reduction in edema and a reduced radiation necrosis as compared to the non-dexamethasone group (Table 1, Figure 4). The data further indicate that dexamethasone treatment reduces the radiation induced metabolic changes leading to neuronal cell damage and chronic inflammatory reaction (Discussion, para 4).

22. Tada et al do not teach contacting an individual subjected to cranial irradiation with a NSAID.

23. The teachings of Plevova are set forth above.

24. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to substitute the use of dexamethasone for reducing loss of neurogenesis capacity in subjects with cranial irradiation as taught by Tada et al., for NSAID or indomethacin in the same individual as taught by Plevova and Monje et al. The person of ordinary skill in the art would have been motivated to substitute one for the other because

both dexamethasone and indomethacin are known anti-inflammatory agents, and both agents have been shown to reduce neuroinflammation and ensuing loss of neurogenesis following cranial irradiation in an individual. The person of ordinary skill in the art would have expected success because the cytotoxic and inflammatory effects of irradiation as well as the anti-inflammatory effects of indomethacin were well known at the time the invention was made.

25. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

26. Claims 1, 3-5, 14, and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 955-962, 2002).

27. The teachings of Kondo et al. or Plevova al are set forth above.

28. Kondo et al or Plevova do not teach do not teach contacting the individual with NSAID before or after irradiation.

29. However, since the claims do not specifiy the criticality in the timing (i.e. before or after irradiation) of contacting the individual with NSAID, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art.

As stated in MPEP 2144.05:

The differences in time will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such timing is

critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages". *In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382; Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 UDPQ2d 1843 (Fed. Cir.).*

30. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to determine the optimal timing of contacting an individual with NSAID, i.e. before or after irradiation, in view of the teachings of Kondo et al, Plevova and Monje et al. The person of ordinary skill in the art would have been motivated to perform such tests, because indomethacin has been known to have both a protective and a therapeutic effect on inflammation. The person of ordinary skill in the art would have expected success because the cytotoxic and inflammatory effects of irradiation as well as the anti-inflammatory effects of indomethacin were well known at the time the invention was made.

31. Therefore, the claimed invention as a whole was clearly prima facie obvious over the prior art.

Conclusion

32. No claims are allowed.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571)

272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

34. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

35. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
5 May 2009

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649